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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/855,320	05/14/2001	Robert Bayer	101961-5108-US	1113

43850 7590 08/13/2009

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1652	

MAIL DATE	DELIVERY MODE
08/13/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/855,320	BAYER, ROBERT	
	Examiner	Art Unit	
	GANAPATHIRAMA RAGHU	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *107-112,115,117,119 and 120* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *107-112,115,117,119 and 120* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Application Status

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06/25/09 has been entered.

Amended claims 107-112, 115, 117, 119 and new claim 120 are pending and are under consideration in the instant Office Action.

Objections and rejections not reiterated from previous action are hereby withdrawn.

Withdrawn-Objection to Specification

Previous objections to specification are being withdrawn due to amendments.

Withdrawn-Claim Rejections: 35 USC § 112

Previous rejection of claim 119 rejected under 35 U.S.C. 112, second paragraph, is being withdrawn due to claim amendment.

Previous rejection of claims 107 and 108 and new claims 109-119 depending therefrom rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is being withdrawn due to claim amendments.

Withdrawn -Claim Rejections 35 USC § 102

Previous rejection of claims 107, 109, 110 and 113-118 rejected under 35 U.S.C. 102(b) as being anticipated by Lowe JB[1] (U.S. Patent No.: 5,324,663, date of patent

06/28/94) or Lowe[2] et al., (U.S. Patent No.: 5,770,420, date of patent 06/23/98), is being withdrawn due to claim amendments.

Previous rejection of claims 107, 109, 110 and 113-118 are rejected under 35 U.S.C. 102(e) as being anticipated by Lowe JB[3] (U.S. Patent No.: 6,268,193, date of patent 07/31/01) or Sasaki et al., (U.S. Patent No.: 7,094,530, date of patent 08/22/06, claiming priority to US Application No.: 08/361,306 filed on 11/29/1994), is being withdrawn due to claim amendments.

New-Claim objections

Claims 108-112, 119 and 120 are objected to under 37 CFR 1.75(c) as being in improper form, because a multiple dependent claim shall not serve as a basis for any other multiple dependent claim. Claim 108-111, 119 and 120 depends on claims 107, 115 or 117 which are multiple dependent claims depending on dependent claims 115 and 117. See MPEP § 608.01(n). Accordingly, the claims 108-112, 119 and 120 not been further treated on the merits.

New-Claim Rejections: 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New-Enablement

Claims 107-112, 115, 117, 119 and 120 are rejected under 35 U.S.C. 112, first paragraph. The prior art enables a method of modifying the fucosylation pattern of a recombinant glycopeptide comprising an acceptor moiety for a recombinant eukaryotic FucT-VI or FucT-VII fucosyltransferase, said method comprising contacting said recombinant glycopeptide with a reaction mixture comprising a fucose donor moiety and

a recombinant eukaryotic FucT-VI or FucT-VII fucosyltransferases as taught by the combination of Lowe JB[1] (U.S. Patent No.: 5,324,663, date of patent 06/28/94) or Lowe[2] et al., (U.S. Patent No.: 5,770,420) or Lowe JB[3] (U.S. Patent No.: 6,268,193,) or Sasaki et al., (U.S. Patent No.: 7,094,530) (see below for the rejection under 35 U.S.C. 103(a)). However, the specification does not reasonably provide enablement for any method of modifying the fucosylation pattern of a recombinant glycopeptide comprising an acceptor moiety for any recombinant eukaryotic FucT-VI or FucT-VII fucosyltransferase, said method comprising contacting said recombinant glycopeptide with a reaction mixture comprising a fucose donor moiety and any recombinant eukaryotic FucT-VI or FucT-VII fucosyltransferases from any source including variants and mutants and wherein said recombinant FucT-VI or FucT-VII provides at least 2-, 4- or 8-fold greater fucosylation of said glycopeptides than is achieved under identical conditions using any FucT-V either naturally derived by biochemical means or recombinantly produced FucT-V. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with the claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in

the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 107-112, 115, 117, 119 and 120 are so broad as to encompass for any method of modifying the fucosylation pattern of a recombinant glycopeptide comprising an acceptor moiety for any recombinant eukaryotic FucT-VI or FucT-VII fucosyltransferase, said method comprising contacting said recombinant glycopeptide with a reaction mixture comprising a fucose donor moiety and any recombinant eukaryotic FucT-VI or FucT-VII fucosyltransferases from any source including variants and mutants and wherein said recombinant FucT-VI or FucT-VII provides at least 2-, 4- or 8-fold greater fucosylation of said glycopeptides than is achieved under identical conditions using any FucT-V either naturally derived by biochemical means or recombinantly produced FucT-V. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides to be used in said method of modifying the fucosylation pattern of a recombinant glycopeptide as broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires knowledge and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the encoded proteins' structure relates to its function.

Furthermore, the art teaches the following regarding fucosyltransferases:

i) de Vries et al., (J. Biol. chem., 1995, Vol. 270 (15): 8712-8722, in IDS) teach that structure acceptor specificities and enzyme kinetics for different recombinant fucosyltransferases inherently varies (column 2, page 8712); Table I (page 8713) and the kinetics also varies for any given fucosyltransferase such as soluble and truncated forms (page 8718, column 1).

ii) Seed B., (WO 96/40881, in IDS), teach extensive structural and functional diversity among fucosyltransferases including recombinantly produced fucosyltransferases (page 2).

iii) Rasko et al., (J. Biol. Chem., 2000, Vol. 275 (7): 4988-4994, in IDS), teach extensive structural and functional diversity among fucosyltransferases and further diversity (both structural and functional) among fucosyltransferases that are isolated from different sources for example from microorganism *H.pylori*.

iv) Staudacher E., (Trends Glycosci and Glycobiol., 1996, Vol. 8 (44): 391-408), in IDS), teach vast differences in biochemical properties among cloned human fucosyltransferases (Table III, page 393).

v) Malissard et al., (Biochem Biophys Res Commun., 2000, Vol. 267: 169-173, in IDS) teach that even among cloned and recombinantly produced fucosyltransferase, depending upon the cellular context in which the recombinant fucosyltransferase was produced, the autoglycosylation patterns of the enzyme vary and said patterns determine the activity of the enzyme.

Prieels et al., (J. Biol. Chem., Vol. 256 (20): 10456-10463, in IDS) also demonstrate the naturally derived fucosyltransferases purified by biochemical means have potential contaminants due to co-purification and the activity of said contaminant varies (entire document).

The claims or the specification does not explicitly state whether: FucT-V is naturally derived and isolated by biochemical means or recombinantly produced FucT-V, full-length FucT-V or lacks membrane anchoring domain, whether autoglycosylated?; 2) for comparison of activities of different enzymes the specific activity i.e., purified protein, the concentration of the purified protein with associated activity is required to establish the differences. The prior art clearly teaches that fucosyltransferases isolated by biochemical means reveal the presence of co-purifying proteins having differing activities.

In the light of the above teachings a skilled artisan requires the structure and the source of the fucosyltransferase especially when activities are being compared.

However, in this case the disclosure is limited to a method of modifying the fucosylation pattern of a recombinant glycopeptide comprising an acceptor moiety for a recombinant eukaryotic FucT-VI or FucT-VII fucosyltransferase, said method comprising contacting said recombinant glycopeptide with a reaction mixture comprising a fucose donor moiety and a recombinant eukaryotic FucT-VI or FucT-VII fucosyltransferases as taught by the combination of Lowe JB[1] (U.S. Patent No.: 5,324,663, date of patent 06/28/94) or Lowe[2] et al., (U.S. Patent No.: 5,770,420) or Lowe JB[3] (U.S. Patent No.:

6,268,193,) or Sasaki et al., (U.S. Patent No.: 7,094,530) (see below for the rejection under 35 U.S.C. 103(a)). In view of the great breadth of the claims, amount of experimentation required to make and use the claimed polypeptides and encoding polynucleotides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (for example, see Whisstock et al., Prediction of protein function from protein sequence and structure. Q Rev Biophys. 2003, Aug. 36 (3): 307-340. Review), to practice the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to make and use the full scope of the polypeptides recited by the claimed methods.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is not routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claim, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions or deletions.

It is also noted that the art teaches several examples of how even small changes in structure can lead to changes in function. For example, Witkowski et al. (Biochemistry, 1999, Vol. 38: 11643-116150) teaches that one conservative amino acid substitution transforms a β̃-ketoacyl synthase into a malonyl decarboxylase and

completely eliminates β̃-ketoacyl synthase activity. Seffernick et al. (J. Bacteriol., 2001, Vol. 183 (8): 2405-2410) teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function.

The specification does not support the broad scope of the claims which encompass for any method of modifying the fucosylation pattern of a recombinant glycopeptide comprising an acceptor moiety for any recombinant eukaryotic FucT-VI or FucT-VII fucosyltransferase, said method comprising contacting said recombinant glycopeptide with a reaction mixture comprising a fucose donor moiety and any recombinant eukaryotic FucT-VI or FucT-VII fucosyltransferases from any source including variants and mutants and wherein said recombinant FucT-VI or FucT-VII provides at least 2-, 4- or 8-fold greater fucosylation of said glycopeptides than is achieved under identical conditions using any FucT-V either naturally derived by biochemical means or recombinantly produced FucT-V, because the specification does not establish: (A) regions of the protein structure of any FucT-VI or FucT-VII fucosyltransferase which may be modified without affecting the activity of fucosyltransferase polypeptide having specific activity and biochemical characteristics such as synthetic and hydrolytic activities, the source of the recombinant enzyme; (B) the general tolerance of the fucosyltransferase polypeptide having specific activity and biochemical characteristics to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue or the respective codon in the polynucleotide with an expectation of obtaining the desired biological function; and

(D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claim broadly including any method of modifying the fucosylation pattern of a recombinant glycopeptide comprising an acceptor moiety for any recombinant eukaryotic FucT-VI or FucT-VII fucosyltransferase, said method comprising contacting said recombinant glycopeptide with a reaction mixture comprising a fucose donor moiety and any recombinant eukaryotic FucT-VI or FucT-VII fucosyltransferases from any source including variants and mutants and wherein said recombinant FucT-VI or FucT-VII provides at least 2-, 4- or 8-fold greater fucosylation of said glycopeptides than is achieved under identical conditions using any FucT-V either naturally derived by biochemical means or recombinantly produced FucT-V. The scope of the claim must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any method of modifying the fucosylation pattern of a recombinant glycopeptide is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

New-Written description

Claims 107-112, 115, 117, 119 and 120 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not disclosed in the specification in

such a way as to reasonably convey to one of skilled in the relevant art that the invention(s), at the time the application was filed, had possession of the claimed invention.

Claims 107-112, 115, 117, 119 and 120 are directed to any method of modifying the fucosylation pattern of a recombinant glycopeptide comprising an acceptor moiety for any recombinant eukaryotic FucT-VI or FucT-VII fucosyltransferase, said method comprising contacting said recombinant glycopeptide with a reaction mixture comprising a fucose donor moiety and any recombinant eukaryotic FucT-VI or FucT-VII fucosyltransferases from any source including variants and mutants and wherein said recombinant FucT-VI or FucT-VII provides at least 2-, 4- or 8-fold greater fucosylation of said glycopeptides than is achieved under identical conditions using any FucT-V either naturally derived by biochemical means or recombinantly produced FucT-V.

The recited method of modifying the fucosylation pattern of a recombinant glycopeptide comprises using a genus of polypeptides and the claimed genus is large and variable with the potentiality of many different structures including variants, mutants and recombinants of FucT-VI or FucT-VII fucosyltransferases and from very many different sources. Therefore, many structurally distinct polypeptides are used within the scope of the methods of the claims.

The specification only discloses a method of modifying the fucosylation pattern of a recombinant glycopeptide comprising an acceptor moiety for a recombinant eukaryotic FucT-VI or FucT-VII fucosyltransferase, said method comprising contacting said recombinant glycopeptide with a reaction mixture comprising a fucose donor moiety and

a recombinant eukaryotic FucT-VI or FucT-VII fucosyltransferases as taught by the combination of Lowe JB[1] (U.S. Patent No.: 5,324,663, date of patent 06/28/94) or Lowe[2] et al., (U.S. Patent No.: 5,770,420) or Lowe JB[3] (U.S. Patent No.: 6,268,193,) or Sasaki et al., (U.S. Patent No.: 7,094,530) (see below for the rejection under 35 U.S.C. 103(a)), however no species (structure associated with function) of the recited genus of polypeptides in a method of modifying the fucosylation pattern of a recombinant glycopeptide comprising an acceptor moiety for a recombinant eukaryotic FucT-VI or FucT-VII fucosyltransferase, said method comprising contacting a full-length recombinant glycopeptide with a reaction mixture comprising FucT-VI or FucT-VII fucosyltransferase and a fucose donor moiety has been disclosed.

The genus of polynucleotides and encoded polypeptides as recited in the claimed invention is an extremely large, functionally and structurally variable genus.

Furthermore, the art teaches the following regarding fucosyltransferases:

I. i) de Vries et al., (J. Biol. chem., 1995, Vol. 270 (15): 8712-8722, in IDS) teach that structure acceptor specificities and enzyme kinetics for different recombinant fucosyltransferases inherently varies (column 2, page 8712); Table I (page 8713) and the kinetics also varies for any given fucosyltransferase such as soluble and truncated forms (page 8718, column 1).

ii) Seed B., (WO 96/40881, in IDS), teach extensive structural and functional diversity among fucosyltransferases including recombinantly produced fucosyltransferases (page 2).

iii) Rasko et al., (J. Biol. Chem., 2000, Vol. 275 (7): 4988-4994, in IDS), teach extensive structural and functional diversity among fucosyltransferases and further diversity (both structural and functional) among fucosyltransferases that are isolated from different sources for example from microorganism *H.pylori*.

iv) Staudacher E., (Trends Glycosci and Glycobiol., 1996, Vol. 8 (44): 391-408), in IDS), teach vast differences in biochemical properties among cloned human fucosyltransferases (Table III, page 393).

v) Malissard et al., (Biochem Biophys Res Commun., 2000, Vol. 267: 169-173, in IDS) teach that even among cloned and recombinantly produced fucosyltransferase, depending upon the cellular context in which the recombinant fucosyltransferase was produced, the autoglycosylation patterns of the enzyme vary and said patterns determine the activity of the enzyme.

vi) Prieels et al., (J. Biol. Chem., Vol. 256 (20): 10456-10463, in IDS) also demonstrate the naturally derived fucosyltransferases purified by biochemical means have potential contaminants due to co-purification and the activity of said contaminant varies (entire document).

In the light of the above teachings a skilled artisan requires the structure and the source of the fucosyltransferase especially when activities are being compared.

II. Even highly structurally homologous polypeptides do not necessarily share the same function and many functionally similar proteins will have little or no structural

homology to disclosed proteins. For example, proteins having similar structure have different activities; Witkowski et al., (Biochemistry 38:11643-11650, 1999) teaches that one conservative amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Similarly, i) Wishart et al., (J. Biol. Chem., 1995, Vol. 270(10): 26782-26785) teach that a single mutation converts a novel phosphotyrosine binding domain into a dual-specificity phosphatase and ii) Broun et al., (Science 282:1315-1317, 1998), teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. The art also teaches that functionally similar molecules have different structures; Kisselev L., (Structure, 2002, Vol. 10: 8-9) teach that polypeptide release factors in prokaryotes and eukaryotes have same function but different structures.

Therefore, the claimed genera polypeptides include proteins having widely variable structures, since minor structural changes may result in changes affecting function and no additional information correlating structure with function has been provided.

Many structurally unrelated polypeptides are encompassed by these claims. The specification only discloses exemplary examples in Examples 2 and on pages 44-45 of what is known in the art, however no species (structure associated with function) of the recited genus of polypeptides in a method of modifying the fucosylation pattern of a recombinant glycopeptide comprising an acceptor moiety for a recombinant eukaryotic FucT-VI or FucT-VII fucosyltransferase, said method comprising contacting said

recombinant glycopeptide with a reaction mixture comprising a fucose donor moiety and a eukaryotic FucT-VI or FucT-VII fucosyltransferase has been disclosed, which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of all species within the required genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed. Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

New-Claim Rejections 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 107-112, 115, 117, 119 and 120 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lowe JB[1] (U.S. Patent No.: 5,324,663, date of patent 06/28/94) or Lowe[2] et al., (U.S. Patent No.: 5,770,420, date of patent 06/23/98) or Lowe JB[3] (U.S. Patent No.: 6,268,193, date of patent 07/31/01) or Sasaki et al., (U.S. Patent No.: 7,094,530, date of patent 08/22/06, claiming priority to US Application No.: 08/361,306 filed on 11/29/1994) and in view of de Vries et al., (J. Biol. chem., 1995, Vol. 270 (15): 8712-8722, in IDS), Seed B., (WO 96/40881, in IDS), Rasko et al., (J. Biol. Chem.,

2000, Vol. 275 (7): 4988-4994, in IDS), Staudacher E., (Trends Glycosci and Glycobiol., 1996, Vol. 8 (44): 391-408), in IDS), Malissard et al., (Biochem Biophys Res Commun., 2000, Vol. 267: 169-173, in IDS) and Prieels et al., (J. Biol. Chem., Vol. 256 (20): 10456-10463, in IDS).

Claims 107-112, 115, 117, 119 and 120 are directed to any method of modifying the fucosylation pattern of a recombinant glycopeptide comprising an acceptor moiety for any recombinant eukaryotic FucT-VI or FucT-VII fucosyltransferase, said method comprising contacting said recombinant glycopeptide with a reaction mixture comprising a fucose donor moiety and any recombinant eukaryotic FucT-VI or FucT-VII fucosyltransferases from any source including variants and mutants and wherein said recombinant FucT-VI or FucT-VII provides at least 2-, 4- or 8-fold greater fucosylation of said glycopeptides than is achieved under identical conditions using any FucT-V either naturally derived by biochemical means or recombinantly produced FucT-V.

Lowe JB[1] or Lowe[2] et al., or Lowe JB[3] disclose an isolated polypeptide annotated as FucT-VI and lacking a membrane anchoring domain and to a method for modifying the fucosylation pattern of a recombinant polypeptide and highly purified polypeptide (entire documents).

Specifically, Lowe JB[1] (U.S. Patent No.: 5,324,663) disclose an isolated polypeptide (SEQ ID NO: 14) annotated as FucT-VI having and lacking a membrane anchoring domain and a method for modifying the fucosylation pattern of a recombinant polypeptide as claimed (entire document; especially column 2, lines 25-35; donor moieties, columns 8-10; use of said glycosyltransferase in enzymatic reactions to

produce glycoproteins, glycolipids, oligosaccharides or polysaccharides of interest, column 13; recombinantly produced glycosyltransferase and abundant quantities of purified glycosyltransferase and use of said enzyme in solutions or solid matrix as bioreactors capable of enzymatic synthesis of glycoproteins column 16, lines 5-11; especially fucosyltransferase lacking membrane anchoring domain, columns 19-20; mechanisms for producing purified enzyme by the use of antibody affinity columns or fusion proteins comprising *Staph. aureus* protein A, columns 26-27 and column 46; Example VI cloning, expression of SEQ ID NO: 14 including polypeptide lacking the membrane anchoring domain, purification of expressed enzyme to high purity using affinity columns and fucosyltransferase assays, columns 87-92).

Said reference further teaches both *in vitro* and *in vivo* fucosylation of glycoproteins of interest as indicated by the title of the document " Methods and products for the synthesis of oligosaccharide structures on glycoproteins, glycolipids, or as free molecules.... furthermore, applicants are directed to the following sections of 5,324,663 document.

Column 2: lines 56-60 discloses; "It is another object of this invention to provide these unmodified and modified isolated genes and cDNAs, and to use them, for example in modifying cell surface oligosaccharide structure via gene transfer approaches or via in vitro glycosylation reactions."

Column 8: lines 15-68 discloses; fucosyltransferases, another type of glycosyltransferases are provided by the present invention, are associated with the following linkages: (1) .... Including the linkages (Galβ1, 4GlcNAc-OR or NeuAcα2,

3Galβ1, 4GlcNAc-OR, wherein R is an amino acid, a saccharide, an oligosaccharide or an aglycon group).

Column 10: lines 45-61 discloses; "In another embodiment...The enzyme of the invention transforms the precursor into desired oligosaccharide, polysaccharide, glycolipid, or glycoprotein which is thereby obtained".

Column 13: lines 43-45 discloses; "in another embodiment…These enzymes can be used in bioreactors in *in vitro*, large scale, synthesis of oligosaccharides or glycolipids or for glycosidic modification of proteins and glycoproteins".

Column 16: lines 30-33 discloses; "enzyamtic catalysis is extraordinarily efficient; virtually complete conversion of substrate to product can be achieved. By contrast, chemical synthesis of these structures is a multi-step process; yields at each step may be much less than 100%..."

Specifically, Lowe[2] et al., (U.S. Patent No.: 5,770,420) disclose an isolated polypeptide (SEQ ID NO: 14) annotated as FucT-VI and lacking a membrane anchoring domain and a method for modifying the fucosylation pattern of a recombinant polypeptide as claimed (entire document; especially column 2, lines 25-35; donor moieties, columns 10-12; use of said glycosyltransferase in enzymatic reactions to produce glycoproteins, glycolipids, oligosaccharides or polysaccharides of interest, column 14; recombinantly produced glycosyltransferase and abundant quantities of purified glycosyltransferase and use of said enzyme in solutions or solid matrix as bioreactors capable of enzymatic synthesis of glycoproteins column 13; especially fucosyltransferase lacking membrane anchoring domain, column 21; Example VI

cloning, expression of SEQ ID NO: 14 including polypeptide lacking the membrane anchoring domain, purification of expressed enzyme to high purity using affinity columns and fucosyltransferase assays, mechanisms for producing purified enzyme by the use of antibody affinity columns or fusion proteins comprising *Staph. aureus* protein A, columns 87-93).

Said reference further teaches both *in vitro* and *in vivo* fucosylation of glycoproteins of interest as indicated by the title of the document " Methods and products for the synthesis of oligosaccharide structures on glycoproteins, glycolipids, or as free molecules…. furthermore, applicants are directed to the following sections of 5,770,420 document.

Column 2: lines 46-50 discloses; "It is another object of this invention to provide these unmodified and modified isolated genes and cDNAs, and to use them, for example in modifying cell surface oligosaccharide structure via gene transfer approaches or via in vitro glycosylation reactions."

Columns 9-10: lines 1-68 discloses; fucosyltransferases, another type of glycosyltransferases are provided by the present invention, are associated with the following linkages: (1) …. Including the linkages (Galβ1, 4GlcNAc-OR or NeuAcα2, 3Galβ1, 4GlcNAc-OR, wherein R is an amino acid, a saccharide, an oligosaccharide or an aglycon group).

Columns 13-14: lines 65-68 of column 13 and lines 1-10 of column 14 discloses; "in another embodiment…These enzymes can be used in bioreactors in *in vitro*, large

scale, synthesis of oligosaccharides or glycolipids or for glycosidic modification of proteins and glycoproteins".

Column 15: lines 33-35 discloses; "in another embodiment…These enzymes can be used in bioreactors in *in vitro*, large scale, synthesis of oligosaccharides or glycolipids or for glycosidic modification of proteins and glycoproteins".

Column 18: lines 32-36 discloses; " enzyamtic catalysis is extraordinarily efficient; virtually complete conversion of substrate to product can be achieved. By contrast, chemical synthesis of these structures is a multi-step process; yields at each step may be much less than 100%...".

Similarly, Sasaki et al., disclose an isolated polypeptide annotated as FucT-VII and lacking a membrane anchoring domain and to a method for modifying the fucosylation pattern of a recombinant polypeptide and highly purified polypeptide (entire document) and as discussed above in 102 (b) and 102(e) rejections.

Specifically Lowe JB[3] disclose an isolated polypeptide (SEQ ID NO: 14) annotated as FucT-VI having and lacking a membrane anchoring domain and a method for modifying the fucosylation pattern of a recombinant polypeptide as claimed (entire document; especially column 2, lines 25-35; donor moieties, columns 8-10; use of said glycosyltransferase in enzymatic reactions to produce glycoproteins, glycolipids, oligosaccharides or polysaccharides of interest, column 13; recombinantly produced glycosyltransferase and abundant quantities of purified glycosyltransferase and use of said enzyme in solutions or solid matrix as bioreactors capable of enzymatic synthesis of glycoproteins columns 13-15; especially fucosyltransferase lacking membrane

anchoring domain, column 19; Example VI cloning, expression of SEQ ID NO: 14 including polypeptide lacking the membrane anchoring domain, purification of expressed enzyme to high purity using affinity columns and fucosyltransferase assays, mechanisms for producing purified enzyme by the use of antibody affinity columns or fusion proteins comprising *Staph. aureus* protein A, columns 83-90; recombinantly purified fucosyltransferase isolated with grater than 95%-98% purity with very high specific activity; claims 1-10, columns 123-124).

Specifically, Sasaki et al., (U.S. Patent No.: 7,094,530) disclose an isolated polypeptide (SEQ ID NO: 2) and lacking a membrane anchoring domain and a method for modifying the fucosylation pattern of a recombinant polypeptide as claimed (entire document; especially column 9, lines 15-40; fucosyltransferase lacking membrane anchoring domain, column 27, lines 1-16, columns 45-46; column 34, lines 27-49; activity assays, columns 35-36; industrial applicability, column 54; claims, columns 73-74).

Said reference further teaches; Column 9: lines 8-25 discloses; “Alpha-1, 3-fucosyltransferase produced in accordance with the present invention can be purified using ordinary methods of purifying glycosyltransferases… or purify the same by affinity chromatography”.

Column 9: lines 31-40 discloses; “Carbohydrate chains can be synthesized *in vitro* using Alpha-1, 3-fucosyltransferase of the present invention. For example, GlcNAC in lactosamine structure (Galβ1-4GlcNAc structure) in glycoproteins, glycolipids or oligosaccharides can be provided with α1$\rightarrow$3 linkage".

Column 74: Claim 14 directed to an *in vitro* method of glycosylation.

de Vries et al., (J. Biol. chem., 1995, Vol. 270 (15): 8712-8722, in IDS) teach that structure acceptor specificities and enzyme kinetics for different recombinant fucosyltransferases inherently varies (column 2, page 8712); Table I (page 8713) and the kinetics also varies for any given fucosyltransferase such as soluble and truncated forms (page 8718, column 1).

Seed B., (WO 96/40881, in IDS), teach extensive structural and functional diversity among fucosyltransferases including recombinantly produced fucosyltransferases (page 2).

Rasko et al., (J. Biol. Chem., 2000, Vol. 275 (7): 4988-4994, in IDS), teach extensive structural and functional diversity among fucosyltransferases and further diversity (both structural and functional) among fucosyltransferases that are isolated from different sources for example from microorganism *H.pylori*.

Staudacher E., (Trends Glycosci. and Glycobiol., 1996, Vol. 8 (44): 391-408), in IDS), teach vast differences in biochemical properties among cloned human fucosyltransferases (Table III, page 393).

Malissard et al., (Biochem Biophys Res Commun., 2000, Vol. 267: 169-173, in IDS) teach that even among cloned and recombinantly produced fucosyltransferase, depending upon the cellular context in which the recombinant fucosyltransferase was produced, the autoglycosylation patterns of the enzyme vary and said patterns determine the activity of the enzyme.

Prieels et al., (J. Biol. Chem., Vol. 256 (20): 10456-10463, in IDS) also demonstrate the naturally derived fucosyltransferases purified by biochemical means have potential contaminants due to co-purification and the activity of said contaminant varies (entire document).

Therefore, it would have been obvious to a person of ordinary skill in the art to combine the above teachings to select and employ an highly purified recombinant fucosyltransferase such as FuCT-VI or FucT-VII with desired kinetic properties in the fucosylation reaction, as said combination teaches fucosyltransferases differ in their kinetic properties and furthermore source of the enzyme governs the biochemical property of said fucosyltransferases; for example recombinant *vs*. fucosyltransferase purified by biochemical means and differences in the activity profile of fucosyltransferases obtained from different sources.

However, said references are silent regarding the concentration of said recombinant FucT-VI or FucT-VII fucosyltransferase is at least 1 Unit/ml (as in claim 108) or wherein said full-length recombinant glycopeptide is a clotting factor or Factor VIII or Factor IX (as in claims 111 and 112) or at least about 2mg/ml (as in claims 119 and 120).

It would have been obvious to a person of ordinary skill in the art to combine the above teachings to reconstitute the expressed polypeptides in a buffer system to any required concentration such as 50mU or at least 2mg/ml for the assay of the enzymatic activity of FucT-VI or FucT-VII fucosyltransferase enzymes and the use of said enzymes in method for modifying the fucosylation pattern of any recombinant polypeptide such as

clotting factor or Factor VIII or Factor IX. Said references teach the isolation and purification of FucT-VI or FucT-VII fucosyltransferase enzymes, said purity in the range of 95%-98%, the protein concentration of said enzymes such as ug/ul, enzyme assays, methods for glycosylation of products of interest and determining the efficiency of glycosylation by said enzymes in said glycosylated products. Therefore a skilled artisan based on the knowledge and information provided in said teachings will certainly be able to determine the specific concentration i.e., Units/ml of said purified enzymes necessary for successfully fucosylating any recombinant polypeptide such as clotting factor or Factor VIII or Factor IX (modify the fucosylation pattern) and to reconstitute the purified enzymes in a suitable buffer to the requisite amount of activity. Motivation to combine the teachings derives from the fact that FucT-VI or FucT-VII fucosyltransferase enzymes are employed in industrial applications for their ability to synthesize various sugar molecules and modification of proteins or sugars by their ability to transfer sugar moieties on acceptor sites of peptide or sugar chain acceptors and furthermore said enzymes when provided with known activity information such as Units/ml will be useful for immediate use and applications without the additional step of determining the specific activity of said enzymes.

The expectation of success is high, because, the disclosure of Lowe JB[1] or Lowe[2] et al., or Lowe JB[4] teach an isolated polypeptide annotated as FucT-VI and lacking a membrane anchoring domain, methods for modifying the fucosylation pattern of any recombinant polypeptide and highly purified polypeptide (entire documents) and similarly, Sasaki et al., disclose an isolated polypeptide annotated as FucT-VII and

methods for modifying the fucosylation pattern of a recombinant polypeptide and highly purified polypeptide (entire document) and the teachings of de Vries et al., Seed B., Rasko et al., Staudacher E., Malissard et al., and Prieels et al., provide guidance for selecting the appropriate fucosyltransferase depending on the experimental need.

Therefore, the above reference renders claims 107-112, 115, 117, 119 and 120 *prima facie* obvious to one of ordinary skill in the art.

Applicants have traversed this rejection with the following arguments:

(1) The alleged *prima facie* obviousness is deficient because the cited references alone, or in any combination, fail to teach each and every element found in the claims. In, particular, the combination of references fail to teach …wherein the fucosyltransferase provides at least 2-fold greater fucosylation of the glycopeptides than is achieved under identical conditions using isolated FucT-V (page 12 of applicants response dated 06/25/09).

(2) Based on the teaching in the Lowe patents one of skill in the art at the time of filing of Lowe patent applications would not have been motivated to pursue the methods as claimed in which fucosyltransferase provides greater fucosylation of the glycopeptides than is achieved under identical conditions using FucT-V…Sasaki fails to cure this deficiency (pages 12-14 of applicants' response dated 06/25/09).

Reply (1) & (2): Applicant's arguments filed on 06/25/09 have been fully considered but they are not persuasive. Examiner takes the position cited references are in congruence with the obviousness rejection and teach all limitations of the instant claims and expectation of success.

Specifically claims as written are directed to method of modifying the fucosylation pattern of a recombinant glycopeptide comprising an acceptor moiety for any recombinant eukaryotic FucT-VI or FucT-VII fucosyltransferase, said method comprising contacting said recombinant glycopeptide with a reaction mixture comprising a fucose donor moiety and any recombinant eukaryotic FucT-VI or FucT-VII fucosyltransferases from any source including variants and mutants and wherein said recombinant FucT-VI or FucT-VII provides at least 2-, 4- or 8-fold greater fucosylation of said glycopeptides than is achieved under identical conditions using **any FucT-V either naturally derived by biochemical means or recombinantly produced FucT-V**.

The claims or the specification does not explicitly state whether: FucT-V is naturally derived and isolated by biochemical means or recombinantly produced FucT-V, full-length FucT-V or lacks membrane anchoring domain, whether autoglycosylated?; 2) for comparison of activities of different enzymes the specific activity i.e., purified protein, the concentration of the purified protein with associated activity is required to establish the differences. The prior art clearly teaches that fucosyltransferases isolated by biochemical means reveal the presence of co-purifying proteins having differing activities.

The cited prior art provides ample guidance with respect to all the elements of the instant invention i.e., the disclosure of Lowe JB[1] or Lowe[2] et al., or Lowe JB[4] teach an isolated polypeptide annotated as FucT-VI and lacking a membrane anchoring domain, methods for modifying the fucosylation pattern of any recombinant polypeptide and highly purified polypeptide (entire documents) and similarly, Sasaki et al., disclose

an isolated polypeptide annotated as FucT-VII and methods for modifying the fucosylation pattern of a recombinant polypeptide and highly purified polypeptide (entire document) and the teachings of de Vries et al., Seed B., Rasko et al., Staudacher E., Malissard et al., and Prieels et al., provide guidance for selecting the appropriate fucosyltransferase depending on the experimental need; structural and functional differences, kinetic properties, substrate diversity, reaction conditions, recombinantly produce enzymes, differences in activities depending on the source of the enzyme.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Therefore, contrary to applicants' arguments, examiner continues to hold the position and is supported in the following eaxminer's arguments:

i) The instant invention is a simple combination of elements taught in the prior art, wherein the elements of prior art are combined to yield predictable results and the choice is from a finite number of identified elements with a highly predictable outcome and expectation of success.

ii) The cited references are in congruence with the obviousness rejection and teach all limitations of the instant claims i. e., meet all the criteria and parameters

(Teaching, Suggestion and Motivation) as defined by *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) and the rationale for TSM test (Teaching, Suggestion and Motivation) according to KSR ruling.

iii) Obviousness does not require an absolute certainty of success but merely a reasonable expectation thereof, so long as the motivation or suggestion to combine the teaching of the cited references is known or disclosed in the prior art and is obvious to one skilled in the art and this is sufficient to establish a *prima facie* case of obviousness.

iv) Moreover, the objectives of the cited references need not be the same as the instant invention to be used in an Obviousness rejection. So long as the motivation or suggestion to combine the teaching of the cited references is known or disclosed in the prior art and is obvious to one skilled in the art. This is sufficient to establish a *prima facie* case of obviousness (MPEP. 2144 [R-6]).

Furthermore, in fact all the elements in the instant invention have been simply assembled from the findings of preexisting art. Contrary to applicants' arguments, the combination has provided the logical progression and understanding of the key elements in the discipline of fucosylation of glycopeptides were well known in the art and the cited references provide all the necessary pieces one would need to apply this basic strategy to determine the fucosylation pattern and kinetics of the reaction.

The basis for the examniner to continue to hold his position is reasoned below; examiner has provided unequivocal evidence for combining the cited references and that the cited references have been properly applied in this obviousness rejection in accordance with the factual enquires set forth in *Graham* **v.** *John Deere Co.*,

383 U.S. 1, 148 USPQ 459 (1966) and the rationale for TSM test (Teaching, Suggestion and Motivation) according to KSR ruling. Furthermore the cited references teach all the limitations of the instant claims.

The cited references render claims 107-112, 115, 117, 119 and 120 *prima facie* obvious to one of ordinary skill in the art when one applies the Teaching, Suggestion and Motivation (TSM) test under the rationale for arriving at a conclusion of obviousness as suggested by the KSR ruling. The rationale applied for this rejection is as follows:

(1) Combining prior art elements according to known method to yield predictable results.

(2) Simple substitution of one known element for another to obtain predictable results.

(3) "Obvious to try"- choosing from a finite number of identified, predictable solution, with a reasonable expectation of success.

The examiner has provided the rationale to support a conclusion that the claims would have been obvious in that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods **with no change in their respective functions**, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. KSR, 550 U.S. at 398 (2007), 82 USPQ2d at 1395; Sakraida v. AG Pro, Inc., 425 U.S. 273, 282, 189 USPQ 449, 453 (1976); Anderson 's-Black Rock, Inc. v. Pavement Salvage Co., 396 U.S. 57, 62-63, 163 USPQ 673, 675 (1969); Great Atlantic & P. Tea Co. v. Supermarket Equipment Corp., 340 U.S. 147, 152, 87 USPQ 303, 306 (1950).

Summary of Pending Issues

The following is a summary of issues pending in the instant application.

1. Claims 108-112, 119 and 120 are objected to under 37 CFR 1.75(c) as being in improper form.

2. Claims 107-112, 115, 117, 119 and 120 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with enablement and written description.

3. Claims 107-112, 115, 117, 119 and 120 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lowe JB[1] (U.S. Patent No.: 5,324,663, date of patent 06/28/94) or Lowe[2] et al., (U.S. Patent No.: 5,770,420, date of patent 06/23/98) or Lowe JB[3] (U.S. Patent No.: 6,268,193, date of patent 07/31/01) or Sasaki et al., (U.S. Patent No.: 7,094,530, date of patent 08/22/06, claiming priority to US Application No.: 08/361,306 filed on 11/29/1994) and in view of de Vries et al., (J. Biol. chem., 1995, Vol. 270 (15): 8712-8722, in IDS), Seed B., (WO 96/40881, in IDS), Rasko et al., (J. Biol. Chem., 2000, Vol. 275 (7): 4988-4994, in IDS), Staudacher E., (Trends Glycosci and Glycobiol., 1996, Vol. 8 (44): 391-408), in IDS), Malissard et al., (Biochem Biophys Res Commun., 2000, Vol. 267: 169-173, in IDS) and Prieels et al., (J. Biol. Chem., Vol. 256 (20): 10456-10463, in IDS).

Conclusion

None of the claims are allowable. Claims 107-112, 115, 117, 119 and 120 are objected/rejected for the reasons identified in the Rejections and Summary sections of this Office Action. Applicants must respond to the objections/rejections in each of the sections in this Office Action to be fully responsive for prosecution.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathirama Raghu whose telephone number is 571-272-4533. The examiner can normally be reached between 8 am-4: 30 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of the application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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